Reduced sleep spindle density in adolescent patients with early-onset schizophrenia compared to major depressive disorder and healthy controls

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Abstract: OBJECTIVES: During adolescence schizophrenia and major depressive disorder (MDD) increasingly emerge. Overlapping symptomatology during first presentation challenges the diagnostic process. Reduced sleep spindle density (SSD) was suggested as a biomarker in adults, discerning patients with schizophrenia from patients with depression or healthy controls (HC). We aimed to compare SSD in early-onset schizophrenia (EOS), with MDD, and HC, and to analyse associations of SSD with symptomatology and neurocognitive measures. METHODS: Automatic sleep spindle detection was performed on all-night high-density EEG (128 electrodes) data of 12 EOS, 19 MDD, and 57 HC (age range 9.8-19), allowing an age- and sex-matching of 1:2 (patients vs. HC). Severity of current symptoms and neurocognitive variables were assessed in all patients. RESULTS: SSD was defined between 13.75 and 14.50 Hz as within this frequency range SSD differed between EOS vs. HC in bin by bin analyses (12-15 Hz). In EOS, SSD was lower over 27 centro-temporal electrodes compared to HC and over 9 central electrodes compared to MDD. Reduced SSD in EOS compared to MDD and HC was accompanied by a high variability of SSD in all adolescents. SSD did not differ between MDD and HC. In the pooled sample of patients, lower SSD was associated with more severe Positive and Negative Symptoms Scale total score, more impaired memory consolidation and processing speed. CONCLUSION: A high variability of SSD in all adolescents may reflect the evolving character of SSD. The association of reduced SSD with the symptom dimension of impaired cognition cuts across diagnostical entities.

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Reduced sleep spindle density in adolescent patients with early-onset schizophrenia compared to major depressive disorder and healthy controls

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ABSTRACT

Objectives: During adolescence schizophrenia and major depressive disorder (MDD) increasingly emerge. Overlapping symptomatology during first presentation challenges the diagnostic process. Reduced sleep spindle density (SSD) was suggested as a biomarker in adults, discerning patients with schizophrenia from patients with depression or healthy controls (HC). We aimed to compare SSD in early-onset schizophrenia (EOS), with MDD, and HC, and to analyse associations of SSD with symptomatology and neurocognitive measures.
Methods: Automatic sleep spindle detection was performed on all-night high-density EEG (128 electrodes) data of 12 EOS, 19 MDD, and 57 HC (age range 9.8–19), allowing an age- and sex-matching of 1:2 (patients vs. HC). Severity of current symptoms and neurocognitive variables were assessed in all patients.
Results: SSD was defined between 13.75 and 14.50 Hz as within this frequency range SSD differed between EOS vs. HC in bin by bin analyses (12–15 Hz). In EOS, SSD was lower over 27 centro-temporal electrodes compared to HC and over 9 central electrodes compared to MDD. Reduced SSD in EOS compared to MDD and HC was accompanied by a high variability of SSD in all adolescents. SSD did not differ between MDD and HC. In the pooled sample of patients, lower SSD was associated with more severe Positive and Negative Symptoms Scale total score, more impaired memory consolidation and processing speed.
Conclusion: A high variability of SSD in all adolescents may reflect the evolving character of SSD. The association of reduced SSD with the symptom dimension of impaired cognition cuts across diagnostical entities.

1. Introduction

Adolescence is a highly dynamic and vulnerable phase of brain maturation during which severe mental disorders such as major depression (MDD) and schizophrenia increasingly emerge (Kessler et al., 2005; Paus et al., 2008). Especially during early phases of the illness, the symptomatology of these two disorders shows substantial overlap complicating the diagnostic process. This age-related challenge may contribute to a longer duration of untreated illness in adolescents compared to adults which in turn worsens outcome (Keshavan et al., 2003; Schimmelmann et al., 2007). Therefore, a biological marker, complementing the clinical diagnostic process in this age-group may pave the way for early intervention and positively influence the course of the disease.

In this context, the repeated finding of reduced sleep spindle density (SSD) in patients affected by schizophrenia seems promising (Manoach et al., 2015). It was first shown in mostly medicated patients chronically affected by the disorder (Ferrarelli et al., 2007) but also replicated in unmedicated patients during an early course of the disease (Manoach et al., 2014). The majority of patients were adults (Ferrarelli et al., 2007, 2010; Göder et al., 2015a; Wamsley et al., 2012), however, first preliminary findings also pointed to reduced SSD in adolescents (Tesler et al., 2015).

The interest in nature and function of sleep spindles, high-amplitude, waxing and waning deflections in the EEG during early deep sleep, has increased (Astori et al., 2013; Castelnovo et al., 2018; De Gennaro and Ferrara, 2003; Dijk, 1995; Manoach and Stickgold, 2019). The key pacemaking circuits of spindles comprise the spindle-generating thalamic reticular nucleus (Ferrarelli and Tononi, 2011; Halassa et al., 2011; Steriade et al., 1987), reciprocal thalamocortical pathways, and the

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cortex. The cortex seems to initiate and maintain synchrony of the oscillation (Piantoni et al., 2013).

In schizophrenia structural alterations of the brain affect the thalamic reticular nucleus (Ferrarelli and Tononi, 2017; Pinault, 2011, 2017; Pratt and Morris, 2015) and the mediodorsal thalamus (Buchmann et al., 2014; Shimizu et al., 2008; Volk and Lewis, 2003) and functional alterations include GABA and glutamate signaling in neural circuitry relevant for spindle generation and maintenance (Catts et al., 2013; Pratt et al., 2017; Thankachan et al., 2019; Théberge et al., 2002).

Sleep spindles have been linked to thalamic gating of sensory information and sleep-related memory consolidation. Both processes possibly bridge impaired sleep spindles, particularly a reduced frequency of spindles per minute (SSD), to key symptom domains affected in schizophrenia such as disturbances of self and perception and impaired cognition (Baran et al., 2019; Göder et al., 2015b; Manoach et al., 2015).

Alterations of SSD are not specific for schizophrenia but also present in neurodevelopmental disorders such as autismus spectrum disorders (Godbout et al., 2000) and neurodegenerative disorders such as Alzheimer's disease (Rauchs et al., 2008). Still, a reduced SSD might differentiate patients with schizophrenia from other patients with severe mental disorders with first onset during early or late adolescence (Castelnovo et al., 2016). This promise was based on a study reporting SSD to be the spindle characteristic best separating adult patients with stable chronic schizophrenia from patients with a current or previous depressive episode (Ferrarelli et al., 2007). The non-overlap of SSD between the patient groups was 80.2% whereas no differences for any spindle characteristic were found between adults with a depressive episode and healthy controls (Ferrarelli et al., 2007). In contrast, in one study assessing children and adolescents currently affected by MDD, SSD was lower compared to healthy controls (Lopez et al., 2010). Beside a possible influence of age, sex, and differences in symptomatology and severity of depression at the time of the sleep assessments, methodological aspects regarding the detection of spindles and their topographical distribution may account for those conflicting results (Lustenberger et al., 2015).

Taken together, the specificity of SSD in schizophrenia relative to other major mental disorders such as MDD needs further investigation and studies examining SSD during the crucial developmental window of adolescence are scarce (Clawson et al., 2016).

The present study builds on our preliminary finding of reduced SSD in 9 patients with EOS (Tesler et al., 2015) and aims to investigate SSD in a larger sample of patients with EOS compared to healthy adolescents as well as patients with MDD. In an exploratory analysis, we finally aimed to correlate SSD with specific domains of psychopathology, neurocognitive performance and memory in a pooled sample of adolescent patients affected by EOS or MDD.

2. Methods

2.1. Participants and clinical assessments

Twelve patients meeting criteria for EOS and 19 patients meeting criteria for MDD first single episode or recurrent according to DSM-IV (American Psychiatric Association, 2000) were recruited from in- and outpatient settings at the Department of Child and Adolescent Psychiatry and Psychotherapy of the Psychiatric University Hospital of Zurich, Switzerland. DSM-IV Axis I diagnoses were confirmed using the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) (Sheehan et al., 1998, 2010). The current sample of adolescent patients with EOS also comprises 8 of 9 patients that have previously been described (Tesler et al., 2015). One patient that was included in our preliminary analyses had to be excluded for the current analysis due to a severe medical condition potentially affecting the brain.

Additionally, 57 HC were recruited in ongoing studies in our lab. HC underwent a telephone and questionnaire screening to exclude personal and family history of mental disorders, and use of any psychotropic or other medication affecting the brain. Sleep assessment was conducted under identical conditions compared to the patient groups.

All participants met the following criteria: (1) aged 9–19, (2) IQ > 70, (2) no major medical or neurological condition known to affect the brain, including history of significant head injury, (3) no substance use dependence within the past 6 months, (4) no diagnosed sleep disorder.

Stable treatment with psychotropic medication was not an exclusion criterion in EOS or MDD. For antipsychotic medication the chlorpromazine equivalent was derived (Andreasen et al., 2010). For patients with MDD receiving selective-serotonine receptor inhibitors, a fluoxetine equivalent was derived (Hayasaka et al., 2015).

To assess actual symptom severity and analyse the symptom domains of positive, negative, general, and depressive symptoms within each patient group and across patient groups, we used the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Children's Depression Rating Scale (CDRS) (Keller et al., 2011). Beside PANSS total score and subscores as derived by the structure of the interview such as positive, negative and general symptom scores, we also included a PANSS cognitive factor as derived by a factor analysis of the symptom dimensions in a sample of patients with EOS (Bunk et al., 1999). Clinical and functional impairment were assessed using the Clinical Global Impression Scale (CGI) (Guy, 1976), the Global Assessment of Functioning (GAF) (Hall, 1995). Pubertal status was assessed using the Tanner scale (Carskadon and Acebo, 1993). Parental socioeconomic status was assessed using the Hollingshead socioeconomic state scale (SES) (Hollingshead, 1975).

In adolescents aged <17 the Wechsler Intelligence Scale for Children IV (Laney et al., 2011) was used and in youth aged ≥17 the Wechsler Adult Intelligence Scale Revised (Wechsler, 1997) was used to assess overall cognitive performance. The respective full version was performed in a stable phase of disease within one year of the sleep assessment in all patients. The full version or a short version (Waldmann, 2008) was performed within two weeks of the sleep assessment in HC.

In patients, the Auditory Verbal Learning Test (AVLT, (Helmstaedter and Durwen, 1990; Lezak et al., 2004)) and the Trail Making Test (TMT, (Reitan and Wolfson, 1995, 2004)) part A and B and the ratio of B/A were additionally used to assess verbal learning, memory, and recognition performance, as well as processing speed the morning after the night in our sleep laboratory.

Written informed consent was obtained from all participants aged ≥18 or from the legal guardian of minors, and written assent was obtained from each minor after careful explanation of the study methods and aims. The study was approved by the local ethics committee (Trial number StV 27/07).

2.2. Matching

Patients with EOS (n = 12, mean age ± SD 16.6 ± 1.4 years, range 13.5–17.9 years, 41.7% female) and patients with MDD (n = 19, mean age ± SD 14.9 ± 1.2 years, range 12.5–16.7 years, 63.2% female) differed significantly in age ($p = 0.002$). More females affected by MDD as well as younger mean age at first onset in MDD patients compared to EOS reflect the expected morbidity rates for these two disorders (Gillberg et al., 1986; Kessler and Avenevoli, 2012).

To account for these group differences and to allow matching for age and sex, we excluded the two oldest male patients with EOS in the group comparison of EOS, MDD, and HC.

Variability of sleep characteristics was shown to be high, especially during adolescence (Clawson et al., 2016; Feinberg and Campbell, 2010; Gaudreau et al., 2001). Therefore, we assessed SSD in a large sample of 57 healthy adolescents (mean age ± SD 14.5 ± 2.4 years, range 9.8–19.0, 47.4% female). Out of this pool of HC (9–11 year-old (n = 11), 12–13 year-old (n = 12), 14–15 year-old (n = 17), 16–19 year-old (n = 17)), two individuals could be age- and sex-matched to one patient.

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2.3. Recording and preprocessing of EEG data

One week prior to the study, all participants were instructed to maintain regular sleep-wake schedules according to their habitual bedtimes. Their usual wake-sleep rhythm was monitored with self-reported sleep logs and wrist motor actigraphy (Actiwatch Plus, AW4, Cambridge Neurotechnology, Cambridge, England). Twenty-four hours before sleep recordings, participants were asked to refrain from alcohol and caffeine and to avoid naps. According to visual inspection of the sleep logs, all participants followed these instructions.

All EEG data were collected in the sleep laboratory of the University Children's Hospital Zurich, Switzerland, with a high-density EEG system (Electrical Geodesic Sensor Net for long-term monitoring, 128 channels). The nets were adjusted to the vertex and the cap electrodes were filled with electrolyte gel (electro-gel, Electro-Cap International). Impedances were measured at the beginning of the recording and kept below 50kΩ. Four additional gold electrodes (Grass Technologies, West Warwick, RI, USA) were attached to the chin (EMG) and earlobes (reference for visual scoring). The sleep episode of each individual was scheduled according to habitual bedtimes. EEG recordings were sampled at 500 Hz (filtered between 0.01 and 200 Hz) and referenced to the vertex (Cz). The data was band-pass filtered between 0.5 and 50 Hz and downsampled to 128 Hz. Sleep stages were scored for 20-s epochs according to standard criteria (Iber and Iber, 2007). All scored nights were reviewed by a *sec*ond sleep expert to assure concordance of the scoring within and between individuals.

Artefacts were rejected on a 20 sec basis after visual inspection and if power exceeded a threshold based on a mean power value in the 0.75–4.5 and 20–30 Hz bands (Huber et al., 2000). The data was re-referenced to the average reference of all good quality EEG channels above the ears (n = 109; of these, on average, 3 channels per individual were of insufficient quality).

2.4. Spindle detection

Automatic sleep spindle detection was performed according to an established algorithm (Ferrarelli et al., 2007).

We focussed on the first hour of artefact-free NREM sleep because it includes the same number of epochs for all participants and constitutes one of the most consolidated parts of sleep. The first high-density EEG study in adult patients with schizophrenia and with a history of depression also assessed sleep spindles in the first sleep episode increasing comparability of the results (Ferrarelli et al., 2007). In contrast, subsequent studies mostly included all-night NREM sleep data to assess SSD (Manoach et al., 2015). Two of our young EOS patients did not tolerate the EEG net during the whole night, hampering our possibilities to additionally assess and compare all-night data. The EEG signal was band-pass filtered between 12 and 15 Hz. A sleep spindle was detected in the rectified signal if the signal amplitude exceeded an upper threshold that was defined relative to the mean signal amplitude. An upper threshold of 5 times the mean signal was determined to result in the best spindle detection after visual inspection of spindle density values that were comparable with previous studies (Dijk, 1995; Lustenberger et al., 2014; Nicolas et al., 2001). Beginning and end of sleep spindles were set when the signal around the peak amplitude dropped below a lower threshold of 2 times the mean signal. We further focussed our analysis on SSD, the number of sleep spindles per min NREM sleep. In a next step, SSD was plotted for each frequency bin between 12 and 15 Hz and channel (128 electrodes) (Lustenberger et al., 2015).

2.5. Statistics

Assessing continuous variables of demographic or clinical characteristics and sleep structure comparing two groups, nonparametric Mann-Whitney *U* tests was chosen, because of non-normal distribution of the data. Accordingly, assessing these variables comparing three groups, Kruskal Wallis was chosen and for significant differences, post hoc analysis was performed to further assess the direction of difference between the groups. For categorical variables, X^2 statistics or Fisher exact test was used.

For topographical analyses, electrode-wise Student's unpaired *t*-tests were performed to compare SSD (13.75–14.50 Hz, first NREM sleep hour) between two groups. To control for multiple comparison, we defined a cluster of at least seven neighbouring electrodes as previously described by Wilhelm et al. (Wilhelm et al., 2014). In short, the threshold of seven was chosen because performing 109 statistic tests would lead to six significant electrodes by chance based on a significance level of 5%. This approach is still conservative because the chance of these seven electrodes clustering nearby is far lower.

One-way analysis of variance (ANOVA) was used to test the effect of patient group on central SSD (cluster of 9 electrodes) and Tukey-Kramer post-hoc tests for pairwise comparisons were applied. Normal distribution of the data was confirmed by Shapiro-Wilk tests.

To assess potential associations of SSD and current psychopathology or neuropsychological variables, we performed correlation analyses in a pooled subset of patients.

All analyses were performed with the software package MATLAB (MathWorks, R2014a/R217b), R i386 (version 3.4.2) and SPSS 22.0.

3. Results

3.1. Reduced SSD in patients with EOS compared to HC

3.1.1. Sample characteristics and sleep structure of patients with EOS and HC

The current diagnoses of patients with EOS (n = 12, mean age ± SD 16.6 ± 1.4 years, range 13.5–17.9, 41.7% female) were according to DSM-IV: schizophrenia (n = 9; 75.0%), schizoaffective disorder (n = 2; 16.7%), and brief psychotic disorder (n = 1; 8.3%). At the time of the sleep recordings, patients were markedly ill (current CGI mean ± SD 4.9 ± 1.4) and had impaired global functioning (current GAF mean ± SD 42.6 ± 19.3). Ten patients (83.3%) received the following antipsychotic medication in descending order: aripiprazole (n = 7, 58.3%), quetiapine (n = 4, 33.3%), olanzapine (n = 1, 8.3%), and clozapine (n = 1, 8.3%). Three patients (25.5%) received a combination of two different antipsychotic agents. The mean chlorpromazine equivalent was 187.6 ± 147.2. Additional medication was lorazepam (n = 3, 25.0%) and biperiden (n = 2, 16.7%).

Age- and sex-matching was possible for 12 EOS vs. 24 HC (Table 1).

We examined visually scored sleep variables to evaluate the sleep quality. Sleep quality was good and sleep efficiency was high (>90%) in both groups. Sleep variables and composition of the first hour of NREM sleep did not differ between the groups (Table 1).

3.1.2. Topographical distribution of SSD in patients with EOS compared to HC

When contrasting the plotted SSD for each frequency bin between 12 and 15 Hz and for each channel between patients with EOS and HC, we found significant differences in the fast spindle frequency range between 13.75 and 14.50 Hz after having applied unpaired Student's *t*-tests (data not shown) (Lustenberger et al., 2015). Therefore, we next focused our analysis on this specific frequency range. Considering the topographical distribution of SSD between patients with EOS and HC by testing each electrode separately, SSD was significantly lower over a centro-temporal cluster of 27 electrodes (−18.28%) in patients with EOS (Fig. 1).

3.2. Reduced SSD in EOS compared to MDD, and HC

3.2.1. Sample characteristics and sleep structure of EOS, MDD, and HC

The two oldest patients with EOS had to be excluded to achieve an age matching with the patients with MDD. HC were age- and sex-

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Table 1
Sample characteristics and sleep structure variables in patients with EOS compared to HC.

Variable	EOS N = 12		HC N = 24		
	Mean (SD)	n (%)	Mean (SD)	n (%)	p
Demographics					
Age (years)	16.6 (1.4)		16.5 (1.4)		0.68
Sex (female)		5 (41.7)		11 (45.8)	1.00
IQ[a]	98.2 (21.3)		113.1 (15.2)		0.95
Sleep variables					
Sleep latency, min	24.1 (16.6)		16.1 (9.0)		0.14
REM sleep latency, min	152.2 (67.4)		122.5 (45.2)		0.20
WASO, min	22.6 (20.4)		25.0 (17.8)		0.46
Sleep efficiency, %	91.5 (5.5)		91.7 (5.0)		0.90
Composition of time interval including first NREM sleep hour					
Absolute length, min	81.6 (15.7)		78.2 (14.3)		0.58
Wake, %	5.5 (10.6)		3.0 (5.6)		0.60
Sleep stage N1, %	4.0 (4.5)		3.8 (5.2)		0.87
Sleep stage N2, %	34.8 (12.2)		41.4 (14.2)		0.16
Sleep stage N3, %	54.1 (19.7)		50.2 (19.1)		0.53
REM sleep, %	1.7 (4.2)		1.7 (3.5)		0.87

WASO = wake after sleep onset; sleep variables and composition of first NREM sleep hour were derived from visual scoring. For all continuous variables Mann-Whitney *U* Test was used and for the categorical variable X^2 statistics was used to test differences between the groups.
[a] IQ available for 9 patients with EOS and 16 HC.

matched to both, patients with EOS or MDD, in a 2:1 ratio (Table 2). IQ did not differ between the groups (Table 2).

At the time of the sleep recordings, both patient groups did not differ regarding their overall severity of illness according to the CGI (EOS 5.0 ± 1.5 vs. MDD 4.6 ± 0.8 ($p = 0.28$)) or their global functioning (EOS 41.3 ± 20.7 vs. MDD 51.6 ± 9.7 ($p = 0.09$)).

In patients with EOS the mean chlorpromazine equivalent was 187.6 ± 147.2. In patients with MDD the mean fluoxetine equivalent was 25.2 ± 17.1.

Sleep quality was good, sleep efficiency was high (>90%) in all three groups, and overall sleep structure variables did not differ between the groups. The time interval in which the first hour of NREM sleep was detected was longer ($p = 0.03$), the relative amount of time awake ($p = 0.02$) and the relative amount of time spent in sleep stage N1 ($p = 0.03$) were higher in patients with EOS compared to patients with MDD (Table 2). The composition of the first hour of NREM sleep did not differ between patients with EOS and HC, or between patients with MDD and HC (Table 2).

3.2.2. Topographical distribution of SSD in patients with EOS compared to patients with MDD, and HC

Comparing SSD of both patient groups, we found 27.11% lower SSD in EOS compared to MDD patients in the frequency range 13.75–14.50 Hz in the first hour of NREM sleep (Fig. 2). The difference was significant in a central cluster of 9 electrodes (Fig. 2).

Comparing SSD between 10 EOS and 20 age- and sex-matched HC, EOS showed 24.07% lower SSD in a centro-temporal cluster of 25 electrodes (Fig. 2).

In patients with EOS, SSD was not associated with CPZ equivalent ($r = 0.08$, $p = 0.82$). In patients with MDD, SSD was not associated with fluoxetine equivalent ($r = 0.32$, $p = 0.43$).

3.2.3. Comparison of central SSD between EOS, MDD, and HC

Assessing the central cluster of 9 electrodes between the three groups, one-way analysis of variance (ANOVA) revealed a significant effect of group on SSD ($F = 6.19$, $p = 0.008$, Fig. 3). Specifically, patients with EOS showed lower SSD in this central cluster compared to both, patients with MDD ($p = 0.008$), and HC ($p = 0.01$). Patients with MDD did not differ from HC ($p = 0.83$).

3.2.4. Association of the central cluster of SSD with current psychopathology, and neuropsychological variables

Beside the statistical group difference of the cluster of 9 electrodes, we were also interested in the high variability of SSD across the groups and overlapping symptomatology in adolescent patients. Thus, in an exploratory analysis, we pooled the data of both patient groups.

SSD of the cluster of 9 electrodes was not associated with age, overall severity of illness, global functioning, or severity of current depressive symptoms (Table 3). In contrast, SSD was negatively correlated with PANSS total score (Fig. 4) and the sum of the subscale of general symptoms. Likewise, lower SSD was associated with higher impairment of the PANSS cognitive factor (Table 3, Fig. 4). Out of the assessed PANSS scores, the correlation coefficient of SSD and PANSS cognitive factor was highest with $r = -0.56$ ($p = 0.01$). Next, we assessed the associations of the 7 single items included in the PANSS cognitive factor with SSD to explore potential driving or conflicting correlations. Starting with the item with the highest negative correlation, the 7 items and respective correlation coefficients were: "somatic concern" ($r = -0.61$, $p < 0.01$), "unusual thought content" ($r = -0.53$, $p = 0.02$), "difficulty in abstract thinking" ($r = -0.44$, $p = 0.05$), "stereotyped thinking" ($r = -0.42$, $p = 0.07$), "guilt feelings" (-0.32, $p = 0.17$), "mannerisms

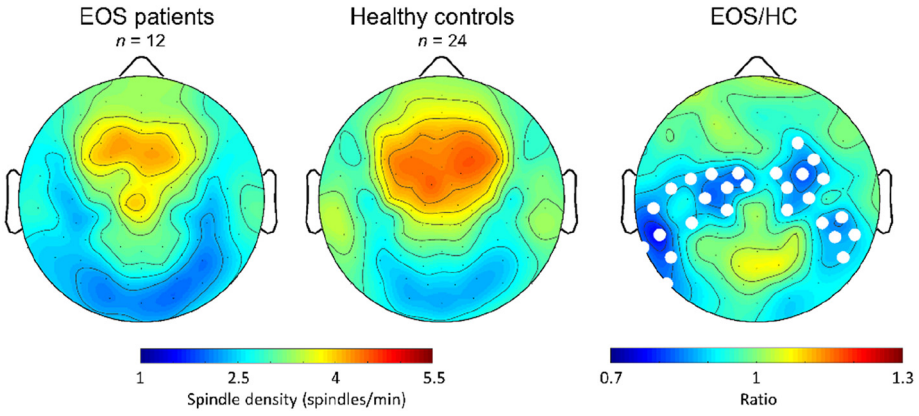

Fig. 1. Topographical distribution of SSD in patients with EOS and HC. Topographical distribution of SSD (spindles/min), frequency range 13.75–14.50 Hz, during the first hour of NREM sleep plotted on the planar projection of the hemispheric scalp model for (a) patients with EOS (n = 12) and (b) age- and sex-matched HC (n = 24). Maxima of spindles are shown in red, minima in blue. Ratio between patients with EOS and HC is shown in (c). White dots represent the significant electrodes of the EEG-cap ($p < 0.05$, one-sided *t*-test). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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Table 2
Sample characteristics and sleep structure variables comparing EOS, MDD, and HC.

Variable	EOS N = 10		MDD N = 10		HC N = 20		EOS vs. MDD vs. HC	
	Mean (SD)	n (%)	Mean (SD)	n (%)	Mean (SD)	n (%)	p	
Demographics								
Age (years)	16.2 (1.4)		15.7 (0.9)		16.2 (1.4)		0.82	
Sex (female)		5 (50)		5 (50)		10 (50)	1.00	
IQ[a]	95.3 (20.7)		113.7 (10.7)		113.0 (16.8)		0.09	
Sleep variables								
Sleep latency, min	20.8 (9.8)		14.3 (11.7)		15.2 (8.3)		0.14	
REM sleep latency, min	141.9 (69.9)		103.5 (26.9)		128.6 (44.5)		0.18	
WASO, min	22.3 (22.8)		12.5 (10.7)		23.7 (17.6)		0.12	
Sleep efficiency, %	92.2 (5.4)		94.0 (5.0)		92.1 (5.0)		0.33	
Composition of time interval including first NREM sleep hour								
Absolute length, min	82.9 (16.8)		70.5 (5.3)		75.9 (9.2)		**0.03**	EOS > MDD
Wake, %	6.4 (11.5)		0.2 (0.3)		2.2 (2.6)		**0.02**	EOS > MDD
Sleep stage N1, %	4.3 (4.8)		0.5 (0.8)		3.3 (4.5)		**0.03**	EOS > MDD
Sleep stage N2, %	34.0 (13.1)		30.6 (16.3)		42.1 (15.1)		0.12	
Sleep stage N3, %	53.5 (21.3)		67.4 (18.3)		51.3 (19.3)		0.11	
REM sleep, %	2.0 (4.5)		1.3 (3.8)		1.2 (3.2)		0.84	

WASO = wake after sleep onset; Sleep variables and composition of first NREM sleep hour were derived from visual scoring. For all variables Kruskal-Wallis test was used to test for differences between the three groups. For significant group differences, post-hoc analysis showed the direction of the difference between the respective groups.
[a] IQ available for 8 patients with EOS, 10 patients with MDD, 13 HC.

and posturing" ($r = -0.31$, $p = 0.19$), and "tension" ($r = -0.07$, $p = 0.77$).

Assessing the neuropsychological variables, SSD was not associated with overall IQ (Table 3), whereas it showed a negative correlation with AVLT recall (Table 3, Fig. 4) and processing speed (Table 3, Fig. 4).

Considering each patient group separately, correlations between SSD and clinical or neuropsychological variables did not reach level of significance in the EOS group. In the sample of patients with MDD, only the PANSS item "somatic concern" correlated negatively with MDD ($r = -0.78$, $p < 0.01$).

4. Discussion

The present study provides further evidence for the hypothesis that reduced SSD may be detected during an early stage of manifestation of schizophrenia and may be a marker for schizophrenia. Specifically, we show that during adolescence, SSD is significantly reduced over centro-temporal electrodes in patients with EOS compared to HC. Increasing the sample size, our preliminary finding of a reduced SSD in EOS remains stable and is in line with previous studies reporting reduced SSD in adult patients during an early phase or during a chronic and stable phase of the disorder (Ferrarelli et al., 2007; Kaskie et al., 2019; Manoach et al., 2014).

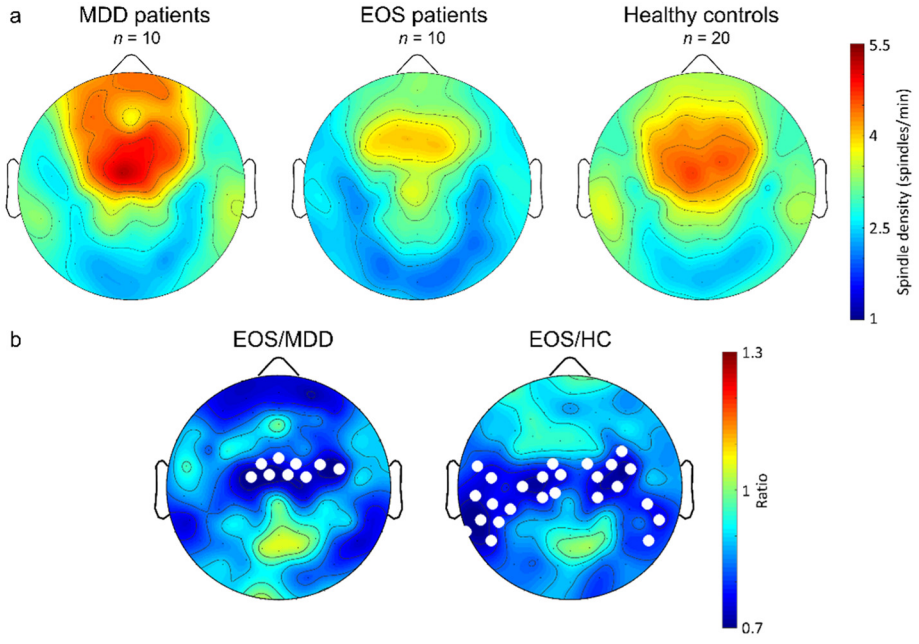

Fig. 2. Topographical distribution of SSD in patients with EOS, with MDD, and in HC. (a) Topographical distribution of SSD (spindles/min), frequency range 13.75–14.50 Hz, during first hour of NREM sleep plotted on the planar projection of the hemispheric scalp model for patients with EOS (n = 10), and age and sex-matched patients with MDD (n = 10) and age- and sex-matched HC (n = 20). Maxima of spindles are shown in red, minima in blue. (b) Ratio between patient groups, as well as between patients with EOS and HC. White dots represent the significant electrodes of the EEG-cap ($p < 0.05$, Student's unpaired two-sided *t*-test). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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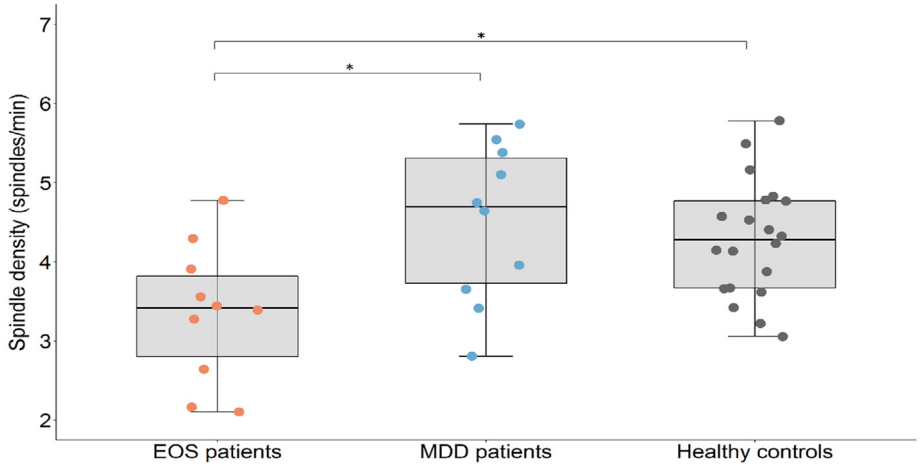

Fig. 3. Central SSD in EOS, MDD, and HC. Boxplots with median and quartiles showing SSD for each group. The whiskers extend to the largest/smallest value. Central SSD was significantly reduced in patients with EOS (red, n = 10) compared to patients with MDD (blue, n = 10, p = 0.01) and HC (black, n = 20, p = 0.02). Central SSD did not differ between patients with MDD and HC (p = 0.79). p-Values according to Tukey-Kramer post-hoc tests following a one-way analysis of variance (ANOVA).

As a diagnostically useful marker, SSD should differentiate between major mental disorders emerging during adolescence. The central cluster that shows a reduced SSD in EOS compared to MDD comprises fewer electrodes compared to findings in adult patients chronically affected by schizophrenia (Ferrarelli et al., 2007, 2010). Likewise, compared to the pronounced non-overlap of the SSD between adult patients with chronic schizophrenia and individuals with a history of MDD, the non-overlap between adolescent patients with EOS and MDD seems less pronounced. From a clinical perspective, the higher variability of SSD within the young patient group may reflect higher heterogeneity of psychopathology during adolescence and different course of disease and outcome. From a neurobiological perspective, variabilities of spindle expression and function paralleling brain maturation had to be expected during adolescence (Clawson et al., 2016; Goldstone et al., 2019; Lindemann et al., 2016; Shinomiya et al., 1999) and may have contributed to overlapping findings across diagnostical entities in this young age group (Manoach and Stickgold, 2019). These findings adjoin increasing evidence of a continuous character of SSD and its potential as a biological marker linking rather symptom dimensions than categorical disorders to thalamocortical disruptions (Baran et al., 2019). Maturational processes and psychosocial factors may be highly dynamic and demanding during adolescence. Thus, the impairment of underlying thalamocortical circuitry relevant for core features of schizophrenia may differ in degree of damage and in topography of cortical and subcortical regions involved compared to adult-onset of the disorder. In this context, it seems interesting that in our patients with EOS, lower SSD was detected over electrodes of a central region and left temporal, sparing prefrontal regions whereas in chronically affected adults with schizophrenia lower SSD was found in prefrontal, left temporal, and a larger centroparietal cluster (Ferrarelli et al., 2010). Suggesting a potential spectrum of increasing decline of SSD with longer duration and chronicity of the disorder and progressive impairment of thalamocortical networks, our finding in adolescent patients may be placed at the lower end, the findings in young early course adults in the middle and the results of older adults with a chronic disorder at the upper end of the spectrum. It would be essential to follow the individuals longitudinally to see whether a reduced SSD precedes worsening of psychopathology and functioning and whether those with the lowest SSD show less favourable outcomes.

Table 3
Correlation analysis of the SSD of the central cluster with a variety of demographic, neuropsychological variables and symptom domains in the pooled sample of both patient groups, EOS and MDD.

	N	R	p
Age	20	−0.16	0.50
Overall severity of illness (CGI)	20	−0.08	0.73
Global functioning (GAF)	20	0.41	0.08
Symptom domain			
Positive, negative, and general symptoms			
PANSS total score	**20**	**−0.50**	**0.03**
PANSS positive sum score	20	−0.42	0.06
PANSS negative sum score	20	−0.42	0.07
PANSS general sum score	**20**	**−0.49**	**0.03**
PANSS EOS cognitive factor	**20**	**−0.56**	**0.01**
Depressive symptoms			
CDRS total	20	−0.42	0.08
Neuropsychological variables			
IQ	18	0.30	0.23
AVLT learning	18	−0.14	0.58
AVLT recall	**18**	**−0.59**	**0.01**
AVLT recognition	18	0.26	0.30
TMT-A	18	−0.01	0.97
TMT-B	18	−0.37	0.14
TMT-B/A, processing speed	**18**	**−0.52**	**0.03**

CGI = Clinical Global Impression Scale, GAF = Global Assessment of Functioning, PANSS= Positive and Negative Symptoms Scale, CDRS=Children's Depression Rating Scale, AVLT = Auditory Verbal Learning Test, TMT = Trail Making Test.
Bolded p-Values <0.05.

Considering the specificity of a reduced SSD for schizophrenia, we confirmed SSD not to differ between patients affected by MDD and HC. This is in line with a study including adults currently affected or with a history of depression (Ferrarelli et al., 2007) and with a study assessing SSD during a 40 min nap in patients with current or remitted MDD (Seeck-Hirschner et al., 2010). In children and adolescents affected by a depressive episode, Lopez and colleagues found lower SSD compared to HC which seems to contrast our finding (Lopez et al., 2010). However, methodological differences limit comparability. Whereas we report SSD using high-density EEG with high spatial resolution focussing on the first hour of NREM sleep, Lopez and colleagues used 8 deviations and showed lower SSD especially in female patients and during later stages of the night. Future studies are warranted assessing all-night data in this young age group and comparing the variability or stability of SSD across the night in EOS to other patient groups.

Increasing evidence suggests that sleep spindles are implicated in memory consolidation and plasticity (Born et al., 2006; Gais et al., 2002). In line with previous studies reporting reduced neurocognitive performance and impaired sleep-dependent learning in patients with schizophrenia (Baran et al., 2018; Manoach et al., 2004, 2010), reduced SSD was associated with impaired memory consolidation and processing speed in our pooled sample of adolescent patients with MDD or EOS.

Sleep spindles have further been shown to be involved in top down processes such as shaping corticothalamic networks in response to

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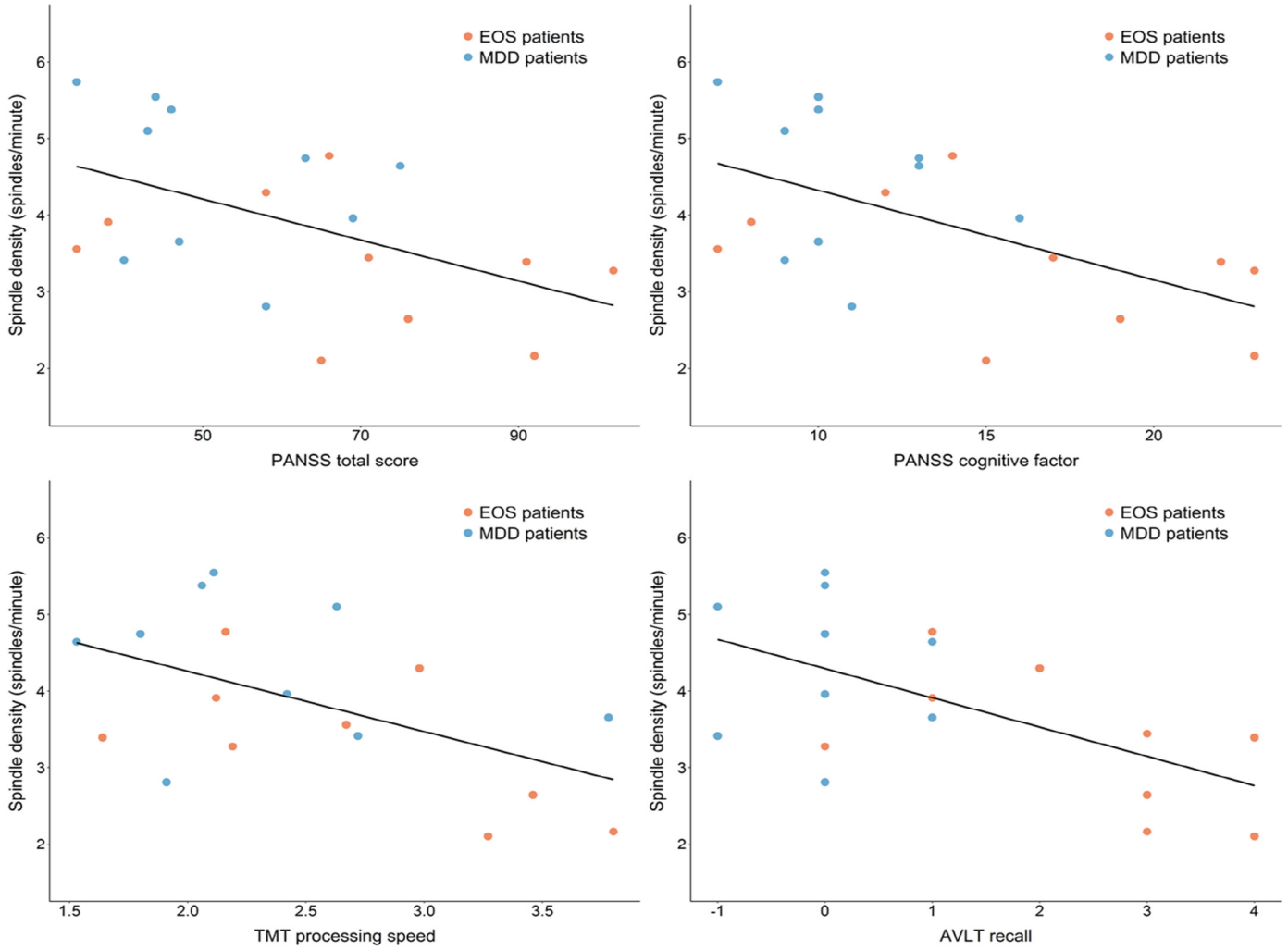

Fig. 4. Linear relationship between central SSD, symptom domains, and neurocognitive measures. Scatterplots of four negative correlations representing the linear relationship of (a) PANSS total sum score, (b) PANSS cognitive factor, (c) Trail Making Test (TMT) processing speed, (d) Auditory Verbal Learning Test (AVLT) recall with the cluster of 9 central electrodes. The single dots show values for each patient (EOS = red; MDD = blue). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

sensory input during daytime as well as bottom up processes such as thalamic gating and cortical map organization throughout maturational processes of body and brain (Buzsáki and Draguhn, 2004; Vukadinovic, 2015). A deficit of sleep spindles in these regions was hypothesized to reflect an impaired activity of the thalamoreticular nucleus which in turn would result in abnormal sensory feedbacks. Especially during the highly dynamic developmental phase of adolescence, a reduced SSD may threaten the fragile balance between predicted and actual sensory feedbacks and irritate sense of agency (Ferrarelli and Tononi, 2017; Pinault, 2011; Shergill et al., 2014; Vukadinovic, 2011, 2015). Indeed, previous mapping of the cortical areas underlying the electrodes with reduced power values in the frequency range 13.75–15 Hz pointed to the primary and secondary somatosensory cortex (Ferrarelli et al., 2007). Comparing the two adolescent patient groups, EOS patients showed significantly lower SSD over 9 central electrodes spanning the premotor cortex. Without mapping, interpretation of these regions that also depend on statistical power should be done with caution. In our exploratory analysis, we assessed associations of the PANSS cognitive factor and found this factor and the items "somatic concern" and "unusual thought content" to be associated with reduced SSD supporting the link of altered SSD with altered body perception and cognitive disturbances.

Previous factor analytic approaches illustrated changing symptom dimensions in patients with EOS across life as assessed by the PANSS (Bunk et al., 1999). The younger the patient with first psychotic episode was, the more often core symptoms such as disturbances of thought and perception were accompanied by non-specific symptoms. In contrast to the emerging PANSS factor that was labelled "cognitive" and comprised items such as stereotyped thinking, difficulty in abstract thinking, unusual thought content and also somatic concern including delusional false beliefs, no separate factor comprising positive symptom items was found in EOS (Bunk et al., 1999). Corresponding to this psychopathological pattern, lower SSD in the central cluster was associated with more severe PANSS total score and general symptoms score whereas the correlations of positive or negative symptom scores did not reach level of significance. In addition to potential statistical issues, the changing symptomatology relative to age at-onset as well as during the course of the disease may contribute to diverging results in different patient groups. In most studies with patients chronically affected by schizophrenia, reduced SSD was associated with more severe positive symptoms (Ferrarelli et al., 2010; Wamsley et al., 2012). In the most recent study in patients with first-onset of schizophrenia, reduced SSD was associated with more severe negative symptoms (Kaskie et al., 2019).

Limitations that have to be considered while interpreting our findings are the cross-sectional and naturalistic character of the study that limits further analysis of temporal and functional associations of sleep spindles. In a hypothesis-driven approach also based on previous findings of our group (Tesler et al., 2015), we focused on EOS compared to HC. We cannot exclude that the frequency range showing largest

differences of SSD may vary comparing EOS to MDD, or MDD to HC. We were able to analyse sleep data of a rather large sample of HC, however, comparable clinical data on psychopathology is missing, so that pooling was restricted to the patient groups. Since the PANSS and the respective subscales are based on theoretical considerations, diverse neuronal underpinnings involving different cortical regions may be associated. Future studies may also include questionnaires rather focusing on specific symptom dimensions. Psychotropic medication was allowed and repeatedly discussed in its effects on sleep characteristics in previous studies. We derived respective equivalents for the medication and did not find any correlations with SSD. A study including a non-schizophrenic psychiatric control groups receiving antipsychotics did not find reduced SSD in this control group (Ferrarelli et al., 2010). Further, including patients with and without medication and controlling for group differences, pointed to no or little impact of antipsychotic medication (Kaskie et al., 2019). GABAergic medication such as lorazepam was also allowed. Previous data suggest that GABAergic agents induce an increase of SSD (Johnson et al., 1983; Wamsley et al., 2013). Still, the three individuals receiving additional lorazepam in the present study did not cluster in the upper or lower end of the spectrum of SSD suggesting no overall consistent impact.

Taken together, focusing on the vulnerable maturational phase of adolescence, our data adds to the hypothesis that SSD may bridge thalamocortical impairment to clinical symptomatology, especially to cognitive deterioration. Subtle cognitive disturbances can be detected long before manifestation of the disorder during the course of the disease cognitive impairment is the most wearing and treatment-refractory symptom domain. Thus, further studies investigating SSD and its associations longitudinally and targeting SSD in innovative treatment approaches around the clock are needed.

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Contributors

R. Huber and S. Walitza designed the study. M. Gerstenberg and M. Furrer undertook the statistical analysis. M. Gerstenberg wrote the first draft of the manuscript. M. Gerstenberg, M. Franscini, and N. Tesler recruited the patients and healthy controls and conducted all assessments. All authors contributed to and have approved the final manuscript.

Conflict of interest

M. Gerstenberg, M. Furrer, N. Tesler, M. Franscini, and R. Huber have nothing to declare. S. Walitza has received lecture honoraria from Eli-Lilly, Opopharma in the last 5 years. Her work was supported by the Swiss National Science Foundation, diff. EU FP7s, Hochspezialisierte Medizin of the Canton of Zurich, Switzerland, Bfarm Germany, ZInEP, Hartmann Müller Stiftung, Olga Mayenfisch in the last 5 years. Outside professional activities and interests are declared under the link of the University of Zurich www.uzh.ch/prof/ssl-dir/interessenbindungen/client/web/.

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